Endogenous retrotransposons and the viral mimicry response during early ovarian tumorigenesis

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Epigenetic therapies alter DNA- and/or histone modifications to facilitate transcription of immunogenic repetitive elements that impart negative selection on cancer cells through ‘viral mimicry’ responses. Paradoxically, functional inactivation the canonical tumor suppressor protein p53, a common initiating event in ovarian high grade serous carcinoma (HGSC), also activates transcription of repetitive elements. Contributions of repetitive element transcription towards cancer initiation, and the mechanisms by which cancer cells evade viral mimicry during tumor initiation remain poorly understood. In this study, we investigate the contributions of misexpressed repetitive elements towards HGSC initiation and progression using HGSC cell-of-origin models and techniques that enable profiling transcriptomic and epigenetic alterations following p53 inactivation. We report that p53 inactivation during HGSC initiation disrupts constitutive heterochromatin to permit transcription of immunogenic repetitive elements capable of activating ‘viral mimicry’ responses. While acute viral mimicry activation diminishes cancer cell fitness, chronic viral mimicry activation promotes epigenetic reprogramming that diminishes cellular immunogenicity as a pro-survival adaptation. This early HGSC immune evasion mechanism that we characterize as ‘viral mimicry conditioning’ can be partially attenuated pharmacologically, offering a potential strategy towards the development of early HGSC interception approaches. Altogether, these results provide context for persistent retrotransposon expression observed throughout HGSC tumorigenesis, and suggest that disruption of viral mimicry conditioning may represent a potential pharmacological approach to intercept early ovarian HGSC.